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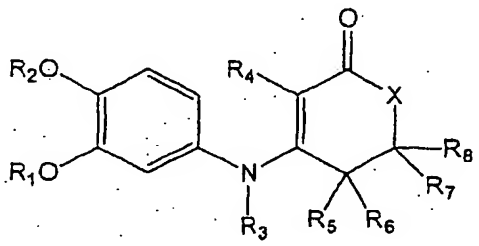
(54) REMEDIES FOR ALLERGIC EYE DISEASES

(57) An agent for the treatment of allergic eye disease containing a 3-anilino-2-cycloalkenone derivative having the formula (I):



(I)

wherein R_1 is an unsubstituted or substituted C_1 to C_8 alkyl group provided that an unsubstituted methyl group is excluded, a C_3 to C_7 cycloalkyl group, a C_6 to C_{10} bicycloalkyl group or an indanyl group, etc., R_2 is a C_1 to C_4 alkyl group, R_3 is a hydrogen atom, a C_1 to C_5 alkyl group, a C_3 to C_7 cycloalkyl group, etc., R_4 is a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group, a halogen atom, etc., R_5, R_6, R_7 and R_8 are independently a hydrogen atom, a C_1 to C_5 alkyl group, etc., X is $-(CR_{11}R_{12})n-$ or $NR_{13}-$, wherein n is 0 to 2, R_{11}, R_{12} and R_{13} are independently a hydrogen atom, a C_1 to C_5 alkyl group, etc.

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Description

TECHNICAL FIELD

[0001] The present invention relates to a novel drug for the treatment of allergic eye disease effective for the treatment of allergic conjunctivitis, vernal catarrh, vernal conjunctivitis, etc. More particularly, the present invention relates to a drug for the treatment of an allergic eye disease containing a 3-anilino-2-cycloalkenone derivative having a phosphodiesterase (PDE) IV (hereinafter sometimes abbreviated as "PDE IV" in this description) inhibitory activity, or a stereoisomer or optical isomer thereof, a salt thereof, or a hydrate or solvate thereof.

BACKGROUND ART

[0002] Allergic conjunctivitis is caused by the binding of antigens such as pollen, house dust with mast cells through antibodies (IgE). The mast cells activated by the antigens release chemical mediators such as histamines to thereby cause conjunctival injection, progression of vascular permeability and infiltration of leukocytes (eosinophils and neutrophils) and, in severe cases, to lead to tissue disorders (Abelson, M.B. et al., *Surv Ophthalmol 38,* p. 115-132, 1993).

[0003] To treat allergic conjunctivitis, antihistamines for suppressing the action of the released histamines, sodium cromoglicate for suppressing the released of chemical mediators such as histamines, adrenocortical steroids, etc. have been used.

[0004] However, antihistamines and sodium cromoglicate cannot be expected to act to suppress the activation of free neutrophils and eosinophils, while adrenocortical steroids have the risk of causing side effects such as glaucoma, cataracts, infection, and therefore, there are limits to their use (Friedlaender M. H., *Ann Allergy Asthma & Immunol. 75*, p. 212-222, 1995).

[0005] From this background, development of a nonsteroidal drug possessing a clear antiinflammatory action has been desired for the treatment of allergic conjunctivitis.

[0006] In recent years, it has become clear that the activity of inflammatory cells such as neutrophils, eosinophils, mast cells is regulated by the second messenger cyclic adenosin monophosphate (cAMP) in the cells (Bourne H. R. et al, *Science,* 184, p. 19-28, 1974). From this fact, it has been considered that drugs increasing the intracellular concentration of cAMP would suppress inflammation. Intensive research therefor is being conducted even now.

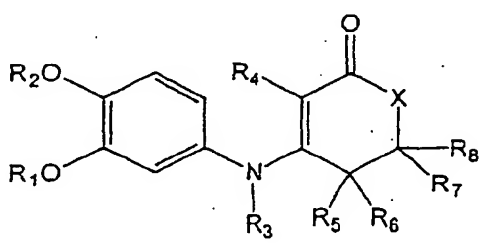
[0007] A phosphodiesterase (PDE) IV inhibitor is expected to inhibit the cAMP hydrolyzing enzyme PDE IV present relatively commonly in inflammatory cells and raise the cAMP concentration in the cells so as to suppress the activation of the inflammatory cells, whereby an antiinflammatory activity is exhibited (Torphy, T. J. et al., Drug *News Perspect,* 6, p. 203-214, 1993, Torphy T. J. and Undem B. J., *Thorax 46,* p. 512-523, 1991).

[0008] Most PDE IV inhibitors are being developed for dealing with allergic diseases such as asthma, atopic dermatitis, rheumatoid arthritis. There are also scattered reports of using the allergic conjunctivitis model for some of these compounds (Revel, L. et al., *Eur J Pharmacol. 229*, p. 45-53, 1992, Newsholme, S. J. and Schwartz, L., *Inflammation 17*, p. 25-31, 1993).

DISCLOSURE OF THE INVENTION

[0009] The inventors found that a 3-anilino-2-cycloalkenone derivative having a PDE IV inhibitory activity alleviates allergic eye diseases, whereby the present invention has been completed.

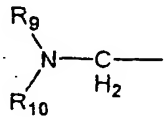
[0010] That is, In accordance with the present invention, there is provided an agent for the treatment of an allergic eye disease, particularly preferably an allergic conjunctivitis treatment agent, comprising a 3-anilino-2-cycloalkenone derivative having the formula (I):



(I)

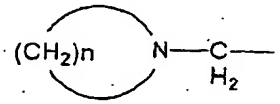
wherein R_1 is an unsubstituted or substituted C_1 to C_8 alkyl group provided that an unsubstituted methyl group is

excluded, a C_3 to C_7 cycloalkyl group, a C_6 to C_{10} bicycloalkyl group, a 3-tetrahydrofuryl group or an indanyl group, R_2 is a C_1 to C_4 alkyl group, R_3 is a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group, a C_3 to C_7 cycloalkyl group or an acyl group, R_4 is a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group, a halogen atom, a group having the formula (II):



(II)

wherein R_9 and R_{10} are independently a C_1 to C_5 alkyl group, or a group having the formula (III):



(III)

wherein n is an integer of 2 to 6, provided that one CH_2 group may be substituted with one hetero atom selected from the group consisting of an oxygen atom, nitrogen atom and sulfur atom, R_5, R_6, R_7 and R_8 are independently a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group or an unsubstituted or substituted phenyl group, X is $-(CR_{11}R_{12})_n-$, wherein R_{11} and R_{12} are independently a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group, or an unsubstituted or substituted phenyl group, and n is an integer of 0 to 2, wherein, when n is 0, the carbonyl carbon atom adjacent to X and the other carbon atom are directly bonded to form a 5-member ring or $-NR_{13}-$ wherein R_{13} is a hydrogen atom or an unsubstituted or substituted C_1 to C_5 alkyl group, a stereoisomer or optical isomer thereof, a pharmacologically acceptable salt, or a hydrate or solvate thereof.

BEST MODE FOR WORKING THE INVENTION

[0011] The present invention will now be explained in detail. Note that, in the description and claims, the singular form is deemed to include the plural form unless the singular is clear from the context.

[0012] The agent for the treatment of allergic eye disease of the present invention contains one of the 3-anilino-2-cycloalkenone derivative of the above general formula (I), the stereoisomer or optical isomer thereof, the pharmacologically acceptable salt thereof, or the hydrate or solvate thereof.

[0013] As R_1 of the compound of the above general formula (I), a C_1 to C_8 straight chain or branched chain alkyl group (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 1,1-dimethylpropyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2-ethylbutyl, n-heptyl, n-octyl, etc.) may be mentioned. These may have a substituent group (e.g., halogen atom; hydroxy group; nitro group; cyano group; amino group; carboxyl group; aryl groups such as phenyl, tolyl, naphthyl; aromatic heterocyclic group such as pyridyl, thiazolyl, thienyl, furyl, quinolyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; haloalkyl group; carbamoyl group; alkoxy group; alkylcarbonyl group, etc.).

[0014] As the C_1 to C_8 alkyl group having a substituent group, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-methylcyclopropylmethyl, 1-phenylcyclopropylmethyl, benzyl, phenethyl, 4-fluorophenethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 2-indanylmethyl, 2-(1-naphthyl)ethyl, 2-(2-pyridyl)ethyl, 2-(4-methyl-5-thiazolyl)ethyl, 2-(benzyloxy)ethyl, 2-(phenethyloxy)ethyl, 2-(methoxy)ethyl, 3-(methoxy)propyl, 4-(methoxy)butyl, 2-(ethoxy)ethyl, 3-(ethoxy)propyl, 2-(butoxyl)ethyl, 2-(cyclopropylmethyloxy)ethyl, 2-(cyclopentyloxy)ethyl, 2-(2-indanyl)ethyl, etc. may be mentioned. However, a methyl group not having a substituent group is excluded from R_1.

[0015] Further, as R_1, a C_3 to C_7 cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.), C_6 to C_{10} bicycloalkyl group [e.g., (1RS,2RS,4SR)bicyclo [2.2.1]hept-2-yl, (1R,2R,4S)bicyclo[2.2.1]hept-2-yl, (1S, 2S,4R)bicyclo[2.2.1]hept-2-yl, etc.], 3-tetrahydrofuryl group, or indanyl group may be mentioned.

[0016] As R_1, preferably a C_4 to C_6 alkyl group; C_4 to C_7 cycloalkyl group; C_6 to C_8 bicycloalkyl group; C_1 to C_5 alkyl group having as a substituent group a phenyl group, naphthyl group, indanyl group, or an unsubstituted or substituted C_3 to C_7 cycloalkyl group; 3-tetrahydrofuryl group, or indanyl group may be mentioned. More preferably, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, 2-(2-indanyl)ethyl, (1RS,2RS,4SR)bicyclo [2.2.1]hept-2-yl, (1R,2R, 4S)bicyclo[2.2.1]hept-2-yl, (1S,2S,4R)bicyclo[2.2.1]hept-2-yl, or 2-indanyl may be mentioned.

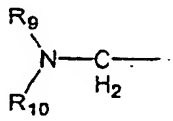
[0017] As R_2 of the compound of the above formula (I), a C_1 to C_4 straight chain or branched chain alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, etc.) may be mentioned, preferably methyl or ethyl may be mentioned, more preferably methyl may be mentioned.

[0018] As R_3 of the compound of the above formula (I), a hydrogen atom, a C_1 to C_5 straight chain or branched chain alkyl group (methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, etc.) may be mentioned. These may also have a substituent group (e.g., halogen atom; hydroxy group; nitro group; cyano group; amino group; carboxyl group; cycloalkyl group; haloalkyl group; carbamoyl group; alkoxy group; alkylcarbonyl group; phenyl, tolyl, naphthyl, or other aryl group; aromatic heterocyclic group containing at least one hetero atom selected from the group consisting of an oxygen atom, nitrogen atom, and sulfur atom (pyridyl, thiazolyl, furyl, thienyl, quinolyl, etc.), etc.) As the C_1 to C_5 alkyl group having a substituent group, for example, benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, furylmethyl, thiazolylmethyl, thienylmethyl, 2-quinolylmethyl, etc. may be mentioned.

[0019] As R_3, a C_3 to C_7 cycloalkyl group (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.) or acyl group (formyl, acetyl, propionyl, benzoyl, etc.) may be mentioned.

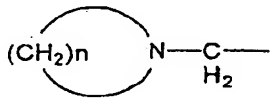
[0020] As R_3, preferably a hydrogen atom; C_1 to C_5 alkyl group; C_3 to C_7 cycloalkyl group; or C_1 to C_2 alkyl group having as a substituent group an aryl group or aromatic heterocyclic group containing at least one hetero atom selected from an oxygen atom, nitrogen atom, and sulfur atom may be mentioned. More preferably a hydrogen atom, methyl, propyl, pentyl, cyclopentyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, benzyl, 2-quinolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, or acetyl may be mentioned.

[0021] As R_4 of the compound of the above formula (I), a hydrogen atom or C_1 to C_5 straight chain or branched chain alkyl group (methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, etc.) may be mentioned. These may also have a substituent group (halogen atom; hydroxy group; nitro group; cyano group; amino group; carboxyl group; cycloalkyl group; haloalkyl group; carbamoyl group; alkoxy group; alkylcarbonyl group; aryl groups such as phenyl, tolyl, naphthyl; aromatic heterocyclic group containing at least one hetero atom selected from an oxygen atom, nitrogen atom and sulfur atom (e.g., pyridyl, thiazolyl, furyl, thienyl, quinolyl, etc.), etc.). Further, as R_4, a halogen atom (chlorine atom, bromine atom, iodine atom, etc.), a group having the following formula (II):



(II)

or the following formula (III) may be mentioned.



(III)

[0022] As R_9 and R_{10} of the above formula (II), a C_1 to C_5 straight chain or branched chain alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, etc.) may be independently mentioned, while as specific examples of the group of the above general formula (II), 1-azetidinylmethyl, 1-pyrrolidinylmethyl, 1-piperidylmethyl, 1-homopiperidylmethyl, 1-piperazinylmethyl, morpholinomethyl, etc. may be mentioned.

[0023] The n of the above formula (III) is an integer of 2 to 6. Further, one CH_2 group may be substituted with one hetero atom selected from an oxygen atom, nitrogen atom and sulfur atom.

[0024] As R_4, preferably a hydrogen atom, halogen atom, C_1 to C_3 alkyl group, dimethylaminomethyl, morpholinomethyl, or benzyl may be mentioned.

[0025] As R_5, R_6, R_7 and R_8 of the above formula (I), a hydrogen atom, C_1 to C_5 straight chain or branched chain alkyl group (methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, etc.), phenyl group, etc. may be independently mentioned. The C_1 to C_5 alkyl group and phenyl group may also have a substituent group (e.g., halogen atom; hydroxy group; nitro group; cyano group; amino group; carboxyl group; alkyl group; cycloalkyl group; haloalkyl group; carbamoyl group; alkoxy group; alkylcarbonyl group; aryl groups such as phenyl, tolyl, naphthyl; aromatic heterocyclic group containing at least one hetero atom selected from an oxygen atom, nitrogen atom, and sulfur atom (e.g., pyridyl, thiazolyl, furyl, thienyl, quinolyl, etc.), etc.) As R_5, R_6, R_7 and R_8, a hydrogen atom or methyl may be preferably mentioned.

[0026] As the X of the above formula (I), $-(CR_{11}R_{12})_n-$ wherein R_{11} and R_{12} are independently a hydrogen atom, substitutable C_1 to C_5 alkyl group, or an unsubstituted or substituted phenyl group, and n is an integer of 0 to 2, where when n is 0, the carbonyl carbon atom adjacent to X and the other carbon atom are directly bonded to form a 5-member ring or $-NR_{13}-$ wherein, as R_{13}, a hydrogen atom or C_1 to C_5 straight chain or branched chain alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, etc.) may be mentioned and may have a substituent group (e.g., halogen atom; hydroxy group; nitro group; cyano group; amino group; carboxyl group; cycloalkyl group; haloalkyl group; carbamoyl group; alkoxy group; alkylcarbonyl group; aryl group such as phenyl, tolyl, naphthyl; aromatic heterocyclic group containing at least one hetero atom selected from an oxygen atom, nitrogen atom and sulfur atom (e.g., pyridyl, thiazolyl, furyl, thienyl, quinolyl, etc.), etc.). As examples of an alkyl group having a substituent group, benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, pyridylmethyl, furylmethyl, and thiazolylmethyl may be mentioned. As X, preferably, $-(CR_{11}R_{12})_n-$ where n is 0 or 1, wherein, when n is 1, R_{11} and R_{12} preferably are independently a hydrogen atom or methyl group or $-NR_{13}-$ wherein R_{13} is a hydrogen atom, C_1 to C_3 alkyl group or benzyl group may be mentioned.

[0027] As specific examples of the compound of the above formula (I), 3-(3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-2-cyclohexen-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-5,5-dimethyl-2-cyclohexen-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-5-methyl-2-cyclohexen-1-one, 2-chloro-3-(3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 2-bromo-3-(3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxyanilino]-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, 3-(4-methoxy-3-phenethyloxyanilino)-2-cyclopenten-1-one, 3-(4-methoxy-3-phenethyloxyanilino)-2-methyl-2-cyclopenten-1-one, 3-(3-cyclohexyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-cyclohexyloxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-(3-cyclopropylmethoxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-cyclopropylmethoxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-(3-butoxyl-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-butoxyl-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxyanilino]-2-cyclohexen-1-one, 3-(3-benzyloxy-4-methoxyanilino)-2-cyclohexen-1-one,4-(3-cyclopentyloxy-4-methoxyanilino)-1,2,5,6-tetrahydropyridin-2-one,1-benzyl-4-(3-cyclopentyloxy-4-methoxyanilino)-1,2,5,6-tetrahydropyridin-2-one, 4-[3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-1,2,5,6-tetrahydropyridin-2-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-2-dimethylaminomethyl-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-2-(4-morpholinomethyl)-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxy-N-methylanilino)-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxy-N-methylanilino)-2-cyclohexen-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(4-pyridylmethyl)anilino]-2-cyclopenten-1-one, 3-(N-acetyl-3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(N-benzyl-3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-2-ethyl-2-cyclopenten-1-one, 2-ethyl-3-[3-(2-indanyloxy)-4-methoxyanilino]-2-cyclopenten-1-one, 2-benzyl-3-(3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-[3-[2-(2-indanyl)ethoxy]-4-methoxyanilino]-2-cyclopenten-1-one, 3-[3-[2-(2-indanyl)ethoxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, 3-[4-methoxy-3-(2,3,4,5-tetrahydrofuran-3-yloxy)anilino]-2-cyclopenten-1-one, 3-[4-methoxy-3-(2,3,4,5-tetrahydrofuran-3-yloxy)anilino]-2-methyl-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-6,6-dimethyl-2-cyclohexen-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-5-phenyl-2-cyclohexen-1-one, 3-(3-cyclopentylmethoxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-cyclopentylmethoxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-[4-methoxy-3-[2-(1-naphthyl)ethoxy]anilino]-2-cyclopenten-1-one, 3-[4-methoxy-3-[2-(1-naphthyl)ethoxy]anilino]-2-methyl-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino)-2-ethyl-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclohexen-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxy-N-methylanilino]-2-methyl-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxyanilino]-2-methyl-2-cyclohexen-1-one, 3-[4-methoxy-3-[(1-phenylcyclopropyl)methoxy]anilino]-2-cyclopenten-1-one, 3-[4-methoxy-3-[(1-phenylcyclopropyl) methoxy]anilino]-2-methyl-2-cyclopenten-1-one, 3-(3-cyclobutylmethoxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-(3-cyclobutylmethoxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-[3-[2-(2-indanyl)ethoxy]-4-methoxyanilino]-2-methyl-2-cyclohexen-1-one, 3-(3-cyclopentylmethoxy-4-methoxyanilino)-2-methyl-2-cyclohexen-1-one, 3-(3-cyclohexyloxy-4-methoxyanilino)-2-methyl-2-cyclohexen-1-one, 3-(N-benzyl-3-cyclohexyloxy-4-methoxyanilino)-2-cyclopenten-1-one,3-[3-cyclohexyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(2-quinolylmethyl) anilino]-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxy-N-propylanilino)-2-cyclopenten-1-one, 3-(N-cyclopentyl-3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(2-pyridylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one3-[3-cyclopentyloxy-4-methoxy-N-(3-pyridylmethyl)anilino]-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxy-N-pentylanilino)-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-methylanilino]-2-cyclohexen-1-one, 3-[N-benzyl-3-(2-indanyloxy)-4-methoxyanilino]-2-cyclohexen-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclohexen-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(2-pyridylmethyl)anilino]-2-cyclohexen-1-one, 2-benzyl-3-(3-cyclopentyloxy-4-methoxyanilino)-

2-cyclohexen-1-one, 3-(3-cyclopentyloxy-4-methoxy-N-methylanilino)-2-methyl-2-cyclopenten-1-one, 3-(N-benzyl-3-cyclopentyloxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(2-quinolylmethyl)anilino]-2-methyl-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(4-pyridylmethyl)anilino]-2-methyl-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(2-naphthylmethyl)anilino]-2-methyl-2-cyclopenten-1-one, 3-(3-cyclopentyloxy-4-methoxyanilino)-2-methyl-2-cyclohexen-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-methylanilino]-2-cyclopenten-1-one, 3-[N-benzyl-3-(2-indanyloxy)-4-methoxyanilino]-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(4-pyridylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(2-quinolylmethyl)anilino]-2-cyclopenten-1-one, 3-[N-benzyl-3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo [2.2.1] hept-2-yloxy]-4-methoxy-N-(2-quinolylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1] hept-2-yloxy]-4-methoxyanilino]-2-cyclohexen-1-one, 3-[N-benzyl-3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-cyclohexen-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxy-N-(4-pyridylmethyl)anilino]-2-cyclohexen-1-one, (-)-3-[3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, (+)-3-[3-[(1S,2S,4R)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, etc. may be mentioned.

[0028] The 3-anilino-2-cycloalkenone derivative of the above formula (I) may be produced by the method described in, for example, Japanese Unexamined Patent Publication (Kokai) No. 11-189577.

[0029] Further, the 3-anilino-2-cycloalkenone derivative of the above formula (I) has asymmetric carbon atoms and, therefore, has optical isomers. These optically pure compounds are obtained by dividing the racemate produced by the method described in the above publication into the optical isomers using high pressure liquid chromatography (HPLC). By recrystallizing the obtained optical isomers when needed, further higher purity optical isomers can be obtained. These optical isomers are also considered to be included in the content of the agent for the treatment of the allergic eye disease of the present invention.

[0030] Further, the salts of the compound of the above formula (I) and the stereoisomer or optical isomer thereof are also included in the content of the agent for the treatment of the allergic eye disease of the present invention. As these salts, pharmacologically acceptable salts are preferable. For example, inorganic acid salts such as hydrochlorate, hydrobromate, hydroiodate, phosphate; and organic acid salts such as oxalate, maleate, fumarate, lactate, malate, citrate, tartarate, benzoate, methanesulfonate, p-toluenesulfonate may be mentioned.

[0031] Further, the agent for the treatment of allergic eye disease of the present invention may also include hydrates or solvates of the 3-anilino-2-cycloalkenone derivative of the above formula (I), its stereoisomer or optical isomer, or their salts. As the solvent of the solvate, methanol, ethanol, isopropanol, butanol, acetone, ethyl acetate, chloroform, etc. may be mentioned.

[0032] The agent for the treatment of allergic eye disease of the present invention may be produced by preparing the 3-anilino-2-cycloalkenone derivative of the above formula (I), its stereoisomer or optical isomer, their pharmaceutically allowable salts, or their hydrates or solvates, alone or mixed with a pharmacologically acceptable vehicle, into a suitable unit form of administration. The composition thereof is determined depending upon the solubility of the compound, the chemical properties, route of administration, the plan of administration, etc.

[0033] As examples of the form of administration, in the case of topical administration, an eye drop, eye ointment, etc. or, in the case of systemic administration, tablets, granules, a dispersion, capsules, a liquid, injection, etc. may be mentioned. In particular, the agent for the treatment of allergic eye disease of the present invention is preferably used in the form of an eye drop.

[0034] The agent for the treatment of allergic eye disease of the present invention is produced by any method known to persons skilled in the art, using the 3-anilino-2-cycloalkenone derivative of the above formula (I), its optical isomer, their pharmacologically acceptable salts, or their hydrates or solvates and a pharmacologially acceptable vehicle.

[0035] Further, as desired or when needed, it is also possible to add various additives usually used when making a preparation such as a suitable binder, lubricant, disintegrant, preservative, buffer, thickener, solution adjuvant, chelating agent, stabilizer, pH adjuster, or isotonic agent.

[0036] For example, in the case of an oral drug, excipients such as lactose, crystalline cellulose, glucose, corn starch, sucrose, sorbitol, erythritol; disintegrants such as calcium carboxymethylcellulose, hydroxypropylcellulose; lubricants such as calcium stearate, magnesium stearate, talc, polyethylene glycol, hydrogenated oil, or another gloss agent, hermectants such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylalcohol, gelatin, gum arabic, and also when needed a surfactant, flavoring agents, etc. may be used to prepare the desired form of administration.

[0037] Further, in the case of a non-oral drug, a dilvents such as water, ethanol, glycerin, propyleneglycol, polyethyleneglycol, agar agar, gum tragacanth may be used, when needed, solution adjuvants (e.g., polyvinylpyrrolidone, polyoxyethylene hydrogenated castor oil, polyethylene glycol, Polysorbate 80, polyoxyethylene monostearate, etc.), preservative (chlorobutanol, sodium dehydroacetate, benzalkonium chloride, cetylpyridium chloride, phenethyl alcohol, p-oxybenzoate esters, benzethonium chloride, etc.), buffer (borate buffer, phosphate buffer, carbonate buffer, acetate

buffer, citrate buffer, etc.), stabilizer (sodium edetate, sodium hydrogensulfite, etc.), pH adjuster (sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, acetic acid, citric acid, phosphoric acid, etc.), isotonic agent (sodium chloride, potassium chloride, glycerin, polyhydric alcohol, sorbitol, mannitol, glucose, etc.), soothing agents, etc. may be used.

[0038] In the case of an eye ointment, a normally used base (ophthamalic white vaseline, plastibase, propeto, etc.) maybe used, while as an additive, liquid paraffin etc. may be mentioned.

[0039] The compound of the above formula (I) usable in the present invention is usually used at a concentration of 0.01 to 3.0 w/v% in the case of an eye drop and is usually used at a concentration of 0.01 to 10.0 w/v% in the case of an eye ointment. Further, when used as a preparation for systemic administration, the dosage, in the case of oral administration, is generally 0.01 to 1000 mg per day, preferably 0.01 to 100 mg per day, but the dosage is more preferably adjusted according to age, condition, symptoms, existence of co-administration, etc.

[0040] The clinical usage and dosage of the agent for the treatment of allergic eye disease of the present invention changes depending on the age, condition, symptoms, etc., but in the case of an eye drop, usually one to two drops are applied from one to six times a day. In the case of an eye ointment, usually a suitable quantity is applied to the conjunctival sac one to two times a day. In the case of oral administration, the dosage is ingested once a day or divided into several times. Further, in the case of an injection, it is injected once a day or divided into several times.

EXAMPLES

[0041] The present invention will now be described in detail by examples and a test example, but the present invention is not limited to these Examples and Test.

Reference Example 1: Method of Production of Optical Isomer

[0042] 1.8 g of the racemic mixture (±)-3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one 1 produced by the method described in Japanese Unexamined Patent Publication (Kokai) No. 11-189577 was dissolved in 1.8L of a mobile phase, then about 70 mg of the sample solution was injected into a column all at once for HPLC.

Column: CHIRALCEL OD (10 cmϕ x 50 cm)
Mobile phase: n-hexane/isopropanol/diethylamine = 90/10/0.1
Flow rate: 190 mL/min

[0043] The fractions of the first peak and the second peak were concentrated in vacuo to obtain an oily residue. Ethanol and n-hexane were added to this, then the mixture was again concentrated in vacuo to obtain powdery optical isomers. The above operation was repeated to obtain from the 1.8 g of the (±)-3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one two types of optical isomers, that is, the (-)-isomer and (+)-isomer, in amounts of 0.70 g and 0.64 g. Further, the structures of the optical isomers were confirmed by comparison with the racemate ^{1}H-NMR.

(-)-isomer: retention time 86 to 98 min, column temperature 40°C
$[\alpha]^{20}_D$ -19°(c=1.00, EtOH)
^{1}H-NMR(400 MHz, $CDCl_3$) δ(ppm):
1.12-1.18(2H,m), 1.21-1.23(1H,m), 1.48-1.54(1H,m), 1.56-1.64(2H,m), 1.68(3H,s), 1.72-1.80(2H,m), 2.35(1H,m), 2.39-2.41(2H,m), 2.51(1H,d,J=4.39Hz), 2.55-2.56(2H,m), 3.85(3H,s), 4.16-4.17(1H,m), 6.41(1H,broads), 6.65(1H,d,J=2.44Hz), 6.69(1H,dd,J=8.79,2.44Hz), 6.83(1H,d,J=8.79Hz)

(+)-isomer: retention time 103 to 121 min, column temperature 40°C
$[\alpha]^{20}_D$ +19°(c=1.00, EtOH)
(±)-isomer ^{1}H-NMR(400 MHz, $CDCl_3$) δ (ppm):
1.12-1.18(2H,m), 1.21-1.23(1H,m), 1.48-1.54(1H,m), 1.56-1.64(2H,m), 1.68(3H,s), 1.72-1.80(2H,m), 2.35(1H,m), 2.39-2.41(2H,m), 2.51(1H,d,J=4.39Hz), 2.55-2.56(2H,m), 3.85(3H,s), 4.16-4.17(1H,m), 6.47(1H,broads), 6.65(1H,d,J=2.44Hz), 6.69(1H,dd,J=8.79,2.44Hz), 6.83(1H,d,J=8.79Hz)

Example 1: Production of Eye Drop

[0044] To sterile water, methylcellulose in an amount of 0.3 g, benzalkonium chloride solution in a small amount, sodium dihydrogenphosphate in an amount of 0.2 g, and sodium hydroxide in a suitable quantity were added and dissolved and then the mixture was filtered to remove dust and bacteria. Dirt- and bacteria-free 3-[3-cyclopentyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one in an amount of 0.5 g was suspended in this solution, then sterile water was added to give a total volume of 100 mL. The suspension thus obtained was filled in a certain amount in a washed, dried, and sterilized eye drop container and a nozzle and cap attached to prepare the eye drop.

Example 2: Production of Eye Ointment

[0045] 0.5 g of 3-[3-cyclopentyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one, 10.0 g of refined lanolin, 80.0 g of ophthalmic white vaseline and 0.5 g of liquid paraffin were taken and adjusted to a total weight 100.0 g to prepare an ointment by the method of production of an eye ointment.

Test Example 1: Alleviating Action for Allergenic Conjunctivitis Model

[0046] For the experiment, Wistar rats (CLEA Japan) were used. The rats were sensitized by intraperitoneal administration of ovalbumin (OA, made by Sigma) in an amount of 100 μg and 10 mg of aluminum hydroxide (Alum, made by Pierce Co.) suspended in 1 mL of physiological saline. Allergic conjunctivitis was induced using rats after 3 weeks from the date of sensitization by dropping into the eyes of 10 μg OA solution prepared by physiological saline to a concentration of 30 mg/mL. The medicine was suspended at a concentration of 1.0 w/v% in physiological saline and dropped into the eyes 10 minutes before OA challenge to induce conjunctivitis (as a positive control drug, diphenhydramine suspended in a concentration of 0.3 w/v% in physiological saline was dropped in the eyes 10 minutes before OA challenge to induce conjunctivitis).

[0047] For the effect of the compound, the number of times of the action of using the hind legs to scratch the eye area (Itch-Scratch response; considered to be an indicator of itchiness) observed in the 20-minute period after dropping the OA was counted and used to find the rate of inhibition of itchiness by the following formula:

Control group: presensitized rats in whose eyes physiological saline is dropped 10 minutes before using OA to induce conjunctivitis
Untreated group: unsensitized rats in whose eyes physiological saline is dropped.
Calculation formula:

$$\text{Inhibition rate (\%)} = 100 - (\text{test substance group} - \text{untreated group})/(\text{control group} - \text{untreated group}) \times 100$$

[0048] Table I shows the results when using for the test substance 3-[3-cyclopentyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one (compound 1), 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one (compound 2), 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-ethyl-2-cyclopenten-1-one (compound 3), (-)-3-[3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one (compound 4), and (+)-3-[3-[(1S,2S,4R)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one (compound 5).

Table I:

Alleviating Activity for Allergic Conjunctivitis Model		
Test substance	No. of animal	Inhibition rate (%)
Compound 1	5	62.9
Compound 2	5	82.7
Compound 3	5	63.5
Compound 4	5	68.6
Compound 5	5	97.1
Diphenhydramine	5	64.6

[0049] As a result, with the eye drops of 1.0 w/v% of the above compounds 1 to 5, an effect of inhibition of the Itch-Scratch response equal to, or greater than, that of the positive control diphenhydramine was observed. It was considered that the edema and itchiness of the eyes appearing in the allergic conjunctivitis model were inhibited.

[0050] Further, with the nontreated group where physiological saline was dropped into the eye, no edema was observed and an Itch-Scratch Response was observed once in one animal out of the four. This is believed to have been induced by the physical stimulus due to the dropping in the eye. In the control group dropping OA into the eye, light to medium edema and Itch-Scratch response was observed in all animal. It was considered that acute allergic conjunc-

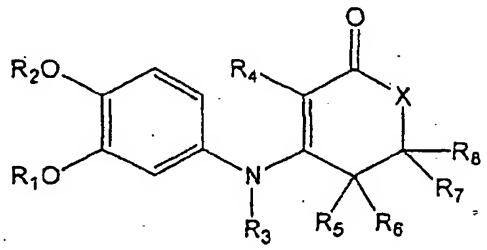
tivitis was induced.

INDUSTRIAL APPLICABILITY

[0051] The agent for the treatment of allergic eye disease of the present invention contains a compound having an activity different from that of existing the agent for the treatment of allergic eye disease (PDE IV inhibitory activity), whereby, a good effect of alleviating allergic conjunctivitis can be obtained and therefore is extremely useful as a new type agent for the treatment of allergic eye disease.

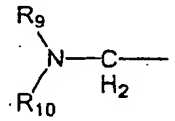
Claims

1. An agent for the treatment of an allergic eye disease comprising a 3-anilino-2-cycloalkenone derivative having the formula (I):



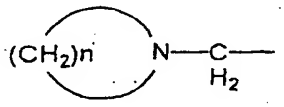
(I)

wherein R_1 is an unsubstituted or substituted C_1 to C_8 alkyl group provided that an unsubstutited methyl group is excluded, a C_3 to C_7 cycloalkyl group, a C_6 to C_{10} bicycloalkyl group, a 3-tetrahydrofuryl group or an indanyl group, R_2 is a C_1 to C_4 alkyl group, R_3 is a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group, a C_3 to C_7 cycloalkyl group or an acyl group, R_4 is a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group, a halogen atom, a group having the formula (II):



(II)

wherein R_9 and R_{10} are independently a C_1 to C_5 alkyl group, or group having the formula (III):



(III)

wherein n is an integer of 2 to 6, provided that one CH_2 group may be substituted with one hetero atom selected from the group consisting of an oxygen atom, nitrogen atom and sulfur atom, R_5, R_6, R_7 and R_8 are independently a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group or an unsubstituted or substituted phenyl group, X is $-(CR_{11}R_{12})_n-$, wherein R_{11} and R_{12} are independently a hydrogen atom, an unsubstituted or substituted C_1 to C_5 alkyl group or an unsubstituted or substituted phenyl group, n is an integer of 0 to 2, where, when n is 0, the carbonylcarbon atom adjacent to X and the other carbon atom are directly bonded to form a 5-member ring, or $-NR_{13}-$ wherein R_{13} is a hydrogen atom or unsubstituted or substituted C_1 to C_5 alkyl group, or a stereoisomer or optical isomer thereof, or pharmacologically acceptable salt thereof, or a hydrate or solvate thereof.

2. An agent for the treatment of an allergic eye disease comprising the 3-anilino-2-cycloalkenone derivative according

to claim 1, or; stereoisomer or optical isomer thereof, pharmacologically acceptable salt thereof, or a hydrate or solvate thereof, wherein, in the formula (I), R_1 is butyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, (1-phenylcyclopropyl)methyl, benzyl, phenethyl, 2-(1-naphthyl)ethyl, 2-(2-indanyl)ethyl, bicyclo[2.2.1]hept-2-yl, 3-tetrahydrofuryl, or 2-indanyl, R_2 is methyl, R_3 is a hydrogen atom, methyl, ethyl, propyl, butyl, pentyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, benzyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-quinolylmethyl, cyclopentyl, or acetyl, R_4 is a hydrogen atom, halogen atom, methyl, ethyl, dimethylaminomethyl, morpholinomethyl or benzyl, R_5, R_6, R_7 and R_8 are independently a hydrogen atom or methyl, X is $-(CR_{11}R_{12})_n-$ wherein R_{11} and R_{12} are independently a hydrogen atom or methyl, and n is 0 or 1, or $NR_{13}-$ wherein R_{13} is a hydrogen atom, a C_1 to C_3 alkyl group, or benzyl.

3. An agent for the treatment of an allergic eye disease comprising the 3-anilino-2-cycloalkenone derivative according to claim 1, or a stereoisomer or optical isomer thereof, a pharmacologically acceptable salt, or a hydrate or solvate, wherein the 3-anilino-2-cycloalkenone derivative is 3-(3-cyclohexyloxy-4-methoxyanilino)-2-methyl-2-cyclopenten-1-one, 1-benzyl-4-(3-cyclopentyloxy-4-methoxyanilino)-1,2,5,6-tetrahydropyridin-2-one, 3-(3-cyclopentyloxy-4-methoxy-N-methylanilino)-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(4-pyridylmethyl)-anilino]-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, 3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-ethyl-2-cyclopenten-1-one, 3-(N-benzyl-3-cyclohexyloxy-4-methoxyanilino)-2-cyclopenten-1-one,3-[3-cyclohexyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one, 3-(N-cyclopentyl-3-cyclopentyloxy-4-methoxyanilino)-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-cyclopentyloxy-4-methoxy-N-(3-pyridylmethyl)anilino]-2-cyclopenten-1-one, 3-[N-benzyl-3-(2-indanyloxy)-4-methoxyanilino]-2-cyclohexen-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(4-pyridylmethyl)anilino]-2-cyclopenten-1-one, 3-[3-(2-indanyloxy)-4-methoxy-N-(2-naphthylmethyl)anilino]-2-cyclopenten-1-one, 3-[N-benzyl-3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-cyclopenten-1-one, 3-[N-benzyl-3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-cyclohexen-1-one3-[3-[(1RS,2RS,4SR)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxy-N-(4-pyridylmethyl)anilino]-2-cyclohexen-1-one, (-)-3-[3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one, or (+)-3-[3-[(1S,2S,4R)-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyanilino]-2-methyl-2-cyclopenten-1-one.

4. An agent for the treatment of an allergic eye disease as claimed in any one of claims 1 to 3, wherein the allergic eye disease is allergic conjunctivitis.

5. An agent for the treatment of an allergic eye disease as claimed in any one of claims 1 to 4, wherein the form of administration is topical administration.

6. An agent for the treatment of an allergic eye disease as claimed in claim 5, wherein the form of administration is an eye drop.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/06912

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K31/122, A61P27/14, 27/02, 37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K31/122

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN), REGISTRY(STN), WPIDS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 11-189577 A (Nikken Chemicals Co., Ltd.), 13 July, 1999 (13.07.99), Full text (Family: none)	1-6
Y	WO 99/18095 A (PERRIER, Helene), 15 April, 1999 (15.04.99), Page 12, line 23 & JP 2001-519344 A Par. No. [0028]	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
12 August, 2002 (12.08.02)	27 August, 2002 (27.08.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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